REMARKS/ARGUMENTS

Claims 1, 3-14, 25-35, 70 and 71 have been examined. Claims 1 and 25 have been amended. No new matter has been added by the amendments as discussed herein below. For convenience, the Examiner's rejections are addressed in the order presented in the November 6, 2009, Office Action. Applicants respectfully request reconsideration of the pending claims in light of the above amendments and the below remarks.

I. Status of the claims

Claims 1 and 25 are amended to recite that only a colorectal mucosal tissue of the subject is contacted with the immunogenic peptide as the means of producing an effective immune response and without subsequent systemic immunization with the composition comprising the chimeric peptide. As such, it is not necessary for an additional subject tissue to be contacted with the composition comprising the chimeric peptide in order to induce the antigen specific systemic and colorectal mucosal cytotoxic T lymphocyte (CTL) response. Support for this amendment is found throughout the specification, for example, page 4, lines 17-28, page 33, lines 33-35; page 34, lines 13-15 and lines 29-33; page 35, lines 20-23; page 36, lines 1-9 and lines 33-35; page 37, lines 11-14 and lines 23-25; page 38, lines 3-9; page 39, lines 21-27. Support for colorectal administration is found throughout the specification, for example, at page 5, line 37 through page 6, line 1 and at page 21, lines 17-21. These amendments add no new matter.

II. Rejections under 35 U.S.C. §103(a)

Claims 1, 3, 4, and 25 remain rejected as allegedly obvious over various combinations of references. To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection.

To establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the

knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference must teach or suggest all the claims limitations. MPEP§2143. Recently, in reviewing this standard, the Supreme Court noted that any analysis supporting a rejection under § 103(a) must be made explicit, and that it is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements in the manner claimed." *KSR Intl Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1396 (U.S. 2007). "This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *Id.*

Claims 1, 3, 4, and 25 remain rejected as allegedly obvious over Klavinskis *et al.* (*J. Immunol.* 157:2521-2527 (1996)) and either Ahlers *et al.*, (*J. Immunol.* 158:3947-3958 (1997)) or Berzofsky *et al.*, (WO 94/26785). The Examiner has alleged that the claims are drawn to a method for inducing a protective rectal mucosal cytotoxic T lymphocyte response in a mammalian subject comprising contacting only a rectal mucosal tissue of the subject with a composition comprising a chimeric peptide having the amino acid sequence of SEQ ID NO: 9. Further, the Examiner alleges that Klavinskis *et al.*, teaches rectal and vaginal immunization by administering an SIV peptide antigen linked to a cholera toxin subunit. This immunization schedule allegedly resulted in cytotoxic T lymphocytes (CTLs) that could be isolated from the rectal mucosa and that were antigen specific. Ahlers *et al.* and Berzofsky *et al.* both allegedly disclose the recited antigenic sequence, SEQ ID NO:9. According to the Examiner, it would have been obvious to one of ordinary skill in the art to modify the method taught by Klavinskis *et al.* to administer the peptide of SEQ ID NO: 9 to a subject. The Examiner has alleged that one of skill would have been motivated to practice the claimed invention by a suggestion of Klavinskis *et al.* that to prevent dissemination of HIV to the regional lymph nodes, an effective vaccine may need to stimulate CTLs in the rectal or genital tract. In addition, the Examiner has alleged that one also would have been motivated by the teachings of Ahlers *et al.* and Berzofsky *et al.* that SEQ ID NO: 9 contains an immunodominant HIV CTL epitope. The Examiner

believes that there would have been a reasonable expectation of success given the findings of Klavinskis *et al.* that mucosal or targeted lymph node immunization generates antigen-specific CTL in the rectal and genital mucosa. As for the use of an adjuvant, the Examiner alleges that Klavinskis *et al.* teaches the use of cholera toxin as an adjuvant and that it was well within the purview of one of ordinary skill in the vaccine arts to administer an antigen with or without an adjuvant. As such, the Examiner has concluded that the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

The Examiner has considered Applicants' prior response and not found it persuasive. In particular, the Examiner has summarized Applicants' response as arguing that the claimed invention is directed to administering antigen to only colorectal tissue; whereas Klavinskis *et al.* disclose rectal or vaginal administration followed by three oral administrations of the vaccine. In response the Examiner alleges that in Klavinskis *et al.* at the time of administering the antigen to mucosal tissue, rectal or colorectal mucosal tissue was the only site of administration and that the oral administrations were carried out months after the rectal administration. The Examiner does not believe that the claims, as currently amended, eliminate further antigen administration at a later time in the future via another route or the same route. The Examiner further believes that the new limitations to the pending claims merely describes what happens at a particular point in time, *i.e.*, at first exposure to the antigen, but does not address what may happen later.

Applicants respectfully disagree, but in order to further expedite prosecution, claims 1 and 25 have been amended to recite " . . . wherein the colorectal mucosal tissue is the only site of contact and without subsequent systemic administration of the composition comprising the chimeric peptide". The claimed method is immunization of a subject by administering SEQ ID NO:9 using only a colorectal tissue as the site of administration of the composition. No subsequent systemic administration of the composition comprising the chimeric peptide is required to induce an antigen specific systemic and mucosal cytotoxic T cell response. In contrast, Klavinskis *et al.* disclose only a combination immunization schedule that results in the induction of antigen specific cytotoxic T cells. That is, Klavinskis *et al.* teach

administration at a rectal or vaginal site, followed subsequently by three oral administrations of the vaccine results in the induction of antigen-specific CTL. There is no disclosure or suggestion that only colorectal or vaginal administration of the composition of Klavinskis *et al.* resulted in any systemic or colorectal mucosal immune response. Klavinskis *et al.* therefore provide no suggestion or motivation to reduce or eliminate the oral administration of the vaccine so as to induce the same or similar immune response that includes an antigen specific CTL response in both the systemic and rectal mucosa. As such, there can be no reasonable expectation of success whether the administration of an antigen to strictly and only rectal mucosa would induce such an immune response. The previously provided declaration from Dr. Berzofsky fully reviews the disclosure of Klavinskis *et al.* and first states that the claimed peptide (SEQ ID NO:9) and the peptide exemplified in the specification (Seq ID NO:2) share the identical immunogenic helper peptide sequence and slightly different variations of the same immunogenic CTL epitope sequence. Thus, Dr. Berzofsky believes that similar immune responses would be generated by both peptides. Further, Dr. Berzofsky states that on reading Klavinskis *et al.*, in his opinion, a skilled artisan would understand that the three additional oral administrations of antigen were **required** to raise an immune response against the antigen. Thus, Klavinskis *et al.* teach away from the claimed invention, which requires administration of antigen only to a colorectal site. The other cited references, Ahlers *et al.* and Berzofsky *et al.*, do not disclose colorectal administration of an HIV antigen. Therefore, the claimed invention is not obvious in view of the cited references.

Further, although Applicants fully believe that claims 1 and 25 limit the administration of the peptide to only colorectal mucosa and do not encompass administration by any systemic means, claims 1 and 25 have been amended to set forth the region and timing of administration with greater particularity. Applicants believe that such amendment limits the administration of the peptide to only colorectal mucosal tissue and does not encompass any subsequent administration of the composition to lymph nodes or other systemic administration.

Applicants respectfully request the Examiner reconsider and withdraw the rejection of claims 1, 3, 4, and 25 as obvious over Klavinskis *et al.* (*J. Immunol.* 157:2521-2527

(1996)) and either Ahlers *et al.*, (*J. Immunol.* 158:3947-3958 (1997)) or Berzofsky *et al.*, (WO 94/26785) in view of the above amendments and remarks.

Claims 1, 5-14, 25-35, 70 and 71 remain rejected as allegedly obvious over Klavinskis *et al.* and either Ahlers *et al.* or Berzofsky *et al.*, or Berzofsky *et al.* (SO 1994/26785) as applied to claims 1, 3, 4, and 25 above, and further in view of Kiyono *et al.* (*Advanced Drug Delivery Reviews* 18:23-51 (1995)). According to the Examiner, the claims are drawn to a method for inducing a protective rectal mucosal cytotoxic T lymphocyte response in a mammalian subject comprising contacting only a rectal mucosal tissue of the subject with a composition comprising a purified soluble antigen, wherein the method further comprises administering a purified cytokine, *e.g.*, GM-CSF, IL-2, IL-7, IL-12, IFNγ or TNF-α, to the subject. The teachings of Klavinskis *et al.* are discussed above, and the Examiner believes that although Klavinskis *et al.* does not teach administering a cytokine to the subject, the Examiner alleges that Ahlers *et al.* teaches immunizing a subject with the peptide of SEQ ID NO:9 and various cytokines. The Examiner further alleges that Ahlers *et al.*, found that GM-CSF synergized with IL-12 for CTL induction, and that TNFα also synergized with IL-12, but by a different mechanism, inducing IFNγ production, thus shifting the response to a Th1 phenotype. IT is also alleged by the Examiner that Ahlers *et al.* suggests that in addition to IL-2, optimum induction of $CD8^+$ CLT *in vivo* requires a combination of cytokines, including GM-CSF and IL-12.

The Examiner alleges that it would have been obvious to one of ordinary skill in the art to modify the method taught by Klavinskis *et al.* to also administer cytokines to the subject with the antigen. It is further alleged by the Examiner that one would have been motivated by the suggestion in Kiyono *et al.* that Th cell-derived cytokines are essential for the induction of appropriate antigen-specific mucosal immune responses and the teachings of Ahlers *et al.* In addition, the Examiner alleges that there would have been a reasonable expectation of success given the findings of Ahlers *et al.* regarding the induction of CTL by cytokines. As such, the Examiner believes that the entire invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

The Examiner has considered Applicants' prior argument and considers that argument non-persuasive. In particular, the Examiner alleges that although Ahlers *et al.* teaches the co-administration of a cytokine in the context of systemic immunization, it would have been reasonable for one of ordinary skill in the art to apply the teachings of Ahlers *et al.* to other administration methods, including mucosal administration. The Examiner alleges that one of ordinary skill in the art would be motivated to do so because Ahlers *et al.* found that in addition to IL-12, optimum induction of $CD8^+$ CTL *in vivo* required a combination of cytokines, including GM-CSF and IL-12. Further, the Examiner has noted that Ahlers *et al.* state that GM-CSF probably acts to enhance antigen presentation and $CD4^+$ help and that because antigen presenting cells are found in both rectal and vaginal mucosa, it would have been reasonable for one of ordinary skill in the art to expect cytokines, *e.g.*, GM-CSF, to aid in the induction of CTL and in antigen presentation in the method of Klavinskis *et al.* where antigen is administered to rectal and vaginal mucosal tissue.

Applicants must again respectfully disagree with the rejection of the Examiner. Ahlers *et al.* and Berzofsky *et al.* disclose only systemic administration of antigen. Kiyono *et al.* disclose various approaches to vaccination with DNA, virus vectors, and other non-peptide constructs. Kiyono *et al.* also make a brief statement about Th-cell derived cytokines and the balance of Th1 and Th2 cell responses. There is no disclosure or suggestion relating to administering cytokines by any method, much less administration or use of non-Th-cell derived cytokines. In particular, there is no disclosure or suggestion of rectal mucosal administration of cytokines. Claims 6, 27, and 71, recite administration of a cytokine to a colorectal mucosal surface. In addition, the specification demonstrates that colorectal administration of IL-12, a non-Th-cell derived cytokine, in combination with SEQ ID NO:2 provides a significant increase in CTL level in both mucosal and systemic sites as compared to colorectal administration of SEQ ID NO:2 without IL-12. *See, e.g.*, specification at page 36, lines 1-9. Still further, intraperitoneal (IP) treatment with IL-12 combined with the colorectal immunization of SEQ ID NO:2 did not increase CTL levels. *See, e.g.*, specification at Example 11, page 45 and Figure 15. As above, according to Dr. Berzofsky, similar immune responses are raised by SEQ ID NO:2

and the claimed SEQ ID NO:9. The Examiner has not addressed either the administration of a protein cytokine via the rectal mucosa or the administration of the cytokine systemically while the peptide antigen is separately administered to a rectal mucosal tissue.

Further, in his declaration, Dr. Berzofsky states that the activity of a cytokine after administration to a colorectal mucosal surface was surprising. Unlike subcutaneous administration, colorectal administration requires the cytokine to retain activity after passing through the hostile environment of the colon. To maintain activity, a cytokine protein must maintain a specific, active structure to allow binding to a cytokine receptor on an appropriate cell. An active cytokine protein requires some minimum of the amino acid sequence to be present in a tertiary structure that is recognized by an appropriate cytokine receptor. According to Dr. Berzofsky, the colon is colonized by bacteria and contains bacterial proteases that can degrade the amino acid sequence of proteins, including cytokines. Thus, according to Dr. Berzofsky, one of skill would not expect the administered cytokine to be remain active after administration to the colon. In addition, Dr. Berzofsky states that, in order to reach cells that express a cytokine receptor, the cytokine had to pass from the colorectal space and through a protective layer of mucus. The passage of the cytokine through the mucus layer and maintenance of activity would not have been expected by those of ordinary skill in Dr. Berzofsky's opinion.

As such, the Examiner has not addressed why one of ordinary skill in the art would have a reasonable expectation that a protein cytokine would be biologically active when administered to the rectal environment. It is well known to the artisan of ordinary skill that a protein antigen does not have to be intact, but can induce an immune response even if cleaved by proteases into peptide fragments. It is also well known that certain peptide fragments can bind to MHC molecules. In contrast, as above, a cytokine must remain sufficiently intact and/or uncleaved to retain its ability to bind to its receptor and maintain cytokine activity. As such, a cytokine is much more at risk of being inactivated by proteases in the colorectal milieu than is the antigen itself. Therefore, there is no reason that one of ordinary skill in the art would have a reasonable expectation that administering a protein cytokine to a colorectal tissue would remain

active once it traverses the rectal mucosa and contacts a cell with an appropriate cytokine receptor.

In view of the above amendments and remarks, reconsideration and withdrawal of the rejection of claims 1, 5-14, 25-35, 70 and 71 as allegedly obvious over Klavinskis *et al.* and either Ahlers *et al.* or Berzofsky *et al.*, or Berzofsky *et al.* (WO 1994/26785) as applied to claims 1, 3, 4, and 25 above, and further in view of Kiyono *et al.* (*Advanced Drug Delivery Reviews* 18:23-51 (1995)) for alleged obviousness is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

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By: Brian W. Poor
Brian W. Poor
Reg. No. 32,928

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 206-467-9600
Fax: 415-576-0300

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